Naval Health Research Center

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SUMMARY

Problem.

Although mental dysfunction becomes increasingly apparent in many individuals infected with the human immunodeficiency virus (HIV+) as they develop symptoms associated with Acquired Immune Deficiency Syndrome (AIDS), it is not well understood when, how, or why HIV+ individuals begin to exhibit cognitive processing deficits. Currently, military personnel who have contracted the HIV virus remain on active duty as long as their immune systems are relatively intact. However, they may be assigned to less strenuous or less attention-demanding positions, since it is not known if neurologic complications during the early stages of infection may affect their job performance.

Objective.

The purpose of this study was to assess the cognitive performance and brain potentials of a pilot group of HIV-infected subjects in an attention-demanding task, in order to understand whether attentional processes are altered by the HIV virus. The overall goal of the project is to develop an objective assessement method that could be used as a routine cognitive "health checkup" to help in deciding whether to allow HIV+ personnel to remain in attention-demanding jobs. ERP results of the study are presented here.

Approach.

Fifteen (eight HIV+ and seven HIV-) subjects were tested using event-related potentials (ERPs) and magnetic event-related fields (ERFs) in an auditory version of a selective attention, evoked response paradigm (Woldorff & Hillyard, 1991). In the selective attention paradigm, two rapid, alternating "oddball" sequences of stimuli are delivered to opposite ears. The subject is instructed to focus his/her attention on only one of the sequences, and to respond to target signals embedded in the attended input sequence, while ignoring all signals in the unattended sequence.

Results.

Two response comparisons were used to study the psychophysiological correlates of cognitive processes in these experiments. The first compared responses to standard (nontarget) stimuli delivered to the attended and unattended ears. For both groups (HIV- and HIV+), ERPs generated to standard stimuli in the attended channel had larger amplitudes in the time frame of the two largest ERP components occurring during the first 200 ms after stimulus onset (N100, P200), suggesting early selective attentional activation did remain intact in the HIV+ group. However, group amplitude differences did appear at approximately 500 ms after stimulus onset. Near this latency, responses of the HIV+ group were more positive than those of the HIV- group. This could possibly be due to HIV-related slowing of attentional processing, resulting in delay in the completion of attentional activation by the attended-channel stimuli.

A second comparison was made between responses to target stimuli delivered to the attended and unattended ears. Responses to attended targets in the HIV- group included a prominent P300 component (at approximately 300 ms), indicating normal cognitive processing according to the ERP literature. However, the ERPs evoked in the HIV+ group by the attended targets contained no discernable P300 components. This result contrasts with previous reports on HIV+ symptomatic and a few asymptomatic subjects which have used a simpler P300 paradigm (the single oddball). In those experiments, increases in latency, and sometimes decreases in amplitude of the P300 have been reported for HIV+ subjects.

Conclusions.

The two electrophysiological differences between HIV+ and HIV- groups, if replicated for a larger patient sample, could lead to an objective, non-invasive method of measuring changes in attentional capabilities of HIV+ personnel.

INTRODUCTION

Purpose. Many of the tasks performed in the Navy and Marine Corps are attention-demanding and require split-second decision-making. It is not known if personnel in the early stages of infection with the human immunodeficiency virus (HIV) have decreased abilities to make time-pressured decisions. Currently, Navy and Marine Corps personnel who are infected with HIV remain on active duty as long as their immune system remain relatively intact. However, for them to continue to work in operational units or to perform some specific duties, a decision by the Chief of Naval Operations or by the Commandant of the Marine Corps (SECNAVINST 5300.30C, 1990) is required, since it is unknown how long HIV-infected individuals remain "fit for duty." The purpose of this study was to evaluate the attention and cognitive abilities of HIV-infected individuals during a high-speed, attention-demanding task, and to determine whether attentional processing deficits are detectable in these individuals.

Two recording methods were used to measure attentional function: 1) event-related potentials (ERPs), i.e., averaged electrical brain responses timelocked to specific experimental stimuli; and 2) event-related fields (ERFs), i.e., averaged magnetic fields evoked in the brain in response to the same stimuli. Both methods (ERPs and ERFs) were used concurrently to record brain function during a dichotic listening task that required selectively focused attention to some of the stimuli. This report presents the ERP findings from the study.

Background. Persons infected with HIV can undergo a host of pathological changes as the virus spreads and suppresses normal immunosystem function (see Sotrel, 1989 for a review). HIV directly affects the central nervous system (CNS), causing subcortical neuropathologies (Sotrel, 1989) to occur which indirectly affect the mental status of infected individuals (Perry, 1990). As HIV infection progresses to the acquired immune deficiency syndrome (AIDS), in many or all patients mental dysfunction becomes apparent and is reflected in degraded performance on neuropsychological tests indicating memory deficits, sluggish intellectual functioning, and social and behavioral problems (Sotrel, 1989) related to CNS deterioration. However, it is unknown how soon after initial HIV infection, and in what ways, individuals begin to decline in cognitive processing capabilities.

Some experts (e.g., Grant et al., 1987; Grant & Heaton, 1990; Wilkie, Eisdorfer, Morgan, Loewenstein, & Szapocznik, 1990) have reported cognitive impairment in a percentage of HIV+ asymptomatic subjects on several neuropsychological tasks that required speed of information processing, verbal memory, psychomotor speed and attention (see Table 1), while others have reported no impairment (e.g., Clifford, Jacoby, Miller, Seyfried, & Glicksman, 1990; Van Gorp, Miller, Satz, & Visscher, 1989). This disparity suggests that either most HIV+ subjects do not become impaired until they are in a more advanced stage of HIV infection, or that some neuropsychological measures may be insensitive to subtle changes in cognitive function until during the course of AIDS proper, neuropathology is so extensive that cognition and behavior are more dramatically affected.

Table 1

Neuropsychological Assessments of HIV*

Impaired**		HIV-		HIV+		AIDS	
		(%)	(prop.)	(%)	(prop.)	(%)	(prop.)
Grant et al.	(1987)	9%	(1/11)	44%	(7/16)	87%	(13/15)
Lunn et al.	(1991)	20%	(4/20)	35%	(7/20)	55%	(11/20)
Perdices & Cooper	(1990)	10%	(1/10)	76.5%	(13/17) [ARC]	53%	(9/17)
Skoraszewski et al.	(1991)	7%	(2/30)	33%	(9/27)	80%	(21/26)
Wilkie et al.	(1990)	0%	(13/13)	22%	(10/46)	---	----
Not Impaired							
Clifford et al.	(1990)	--	(N=50)	--	(N=33)	---	----
Gibbs et al.	(1990)	--	(N=20)	--	(N=20)	25%	(5/20)
Miller et al.	(1990)	3.9%	(30/769)	5.5%	(40/727)	11.9%	(10/84) [ARC]
Selnes et al.	(1990)	--	(N=170)	--	(N=238)	---	----
Van Gorp et al.	(1989)	--	(N=13)	--	(N=14) [ARC]	---	----

* **Neuropsychological tests included:**
Trail-Making, Part A & B - attention, divided attention, psychomotor speed
Grooved Pegboard - psychomotor speed
Finger Tapping - psychomotor speed
Rey Auditory Verbal Learning Test - verbal learning and verbal memory
Wechsler Adult Intelligence Scale-Revised - verbal ability, visuospatial ability, abstraction, attention, & general intellect
Wechsler Memory Scale - attention, verbal learning, & memory

**** verbal memory, psychomotor speed, attention, speed of information processing**
[ARC] = AIDS Related Complex
"--" indicates no percentages or proportions were available

An alternative to cognitive assessment by behavioral performance measures alone is psychophysiological measurement of brain function. One method of measuring brain function is averaging brain electrical responses timelocked to events of interest, producing records known as event-related potentials (ERPs). ERPs can index the dynamic neural state of the brain during rapid information presentation by measuring changes in brain activity following specific stimulus events. ERP waveforms consist of a series of distinct positive-negative components that represent

voltage fluctuations generated in various populations of neurons synchronously activated during or after experimental events (Donchin, Ritter, & McCallum, 1978). Those of primary interest in this study are the largest components generated in the first 400 ms after stimulus onset — normally called the N100 (a negative peak at about 100 ms), P200 (a positive peak at about 200 ms), and P300 (a positive peak at about 300 ms). The first two of these components are known to change both in amplitude and latency as a function of both the physical characteristics of the stimuli (e.g., signal strength, Rapin et al., 1966) and the attentional demands of the task (Näätänen & Picton, 1987). The P300 is ordinarily produced by occasional target (or "oddball") signals that have been given psychological relevance by asking subjects to respond to them (Pritchard, 1981).

ERPs have become a much-used tool in developing an understanding of the effects of HIV on brain function. Comi et al. (1987) have reported slowed visual, somatosensory, and auditory brainstem ERPs in AIDS patients. However, these experiments involve stimuli (checkerboard pattern, median nerve stimulation, or monaural clicks) and subject instructions ("remain quiet") which do not specifically engage subjects' cognitive processes. Similarly, Koralnik et al. (1990) and Cazzullo et al. (1990) reported slowed somatosensory ERPs in relatively healthy (asymptomatic) HIV patients.

In principle, cognitive ERPs could be used to indicate an HIV+ individual's functional state, and could become a clinically useful tool to assess changes in cognitive function during early stages of HIV infection. Some experts (Goodwin, Chiswick, Egan, St. Clair, & Brettle, 1990; and Ollo, Johnson, & Grafman, 1990) using various versions of a simple, relatively undemanding cognitive paradigm (the "oddball" task) have reported reduced amplitude and longer latency P300 components, paralleled by longer reaction times to the target stimuli, in an AIDS subgroup but not in an asymptomatic HIV+

subgroup. Others (Goodin, Aminoff, Chernoff, & Hollander, 1990; Grotemeyer, et al. 1991; Messenheimer, Robertson, Wilkins, Kalkowski, & Hall, 1992) using a similar oddball task, have reported delayed P300s (20 to 60 ms) in some asymptomatic patients. Although these reports indicate that some asymptomatic patients may show performance and ERP differences during the oddball task, we hypothesized that HIV+ asymptomatic subjects might show more substantial differences in demanding tasks involving rapid stimulus presentations.

A research paradigm often used in ERP research that involves rapid processing of auditory stimuli is the selective attention paradigm, in which two rapid, alternating "oddball" sequences of stimuli are delivered to opposite ears. The subject is instructed to focus his/her attention on only one of the sequences, and to respond to target signals embedded in the attended input sequence, while ignoring targets embedded in the unattended sequence. To increase the level of difficulty, the target signals may be made to share several attributes with the standards (e.g., by giving them the same duration or pitch as the standards, but a lower intensity). Under such conditions, the subject's target recognition process becomes slow and attention-demanding (Posner & Petersen, 1990). The more attributes the targets and nontargets share, the higher level of attentional and cognitive involvement needed to distinguish targets from standards. The result is a more difficult and attention-demanding task than the usual single oddball task, one which might raise the likelihood of finding HIV-related differences in performance and ERP components.

Selective attention has been studied extensively using ERPs (Hillyard & Picton, 1987; Hillyard, Hink, Schwent, & Picton, 1973; and Woldorff & Hillyard, 1991). Generally, the amplitude of certain auditory ERP components in response to a given stimulus are enhanced when attention is focused on a channel to which that stimulus belongs. The amplitude enhancements reflect neuronal

processes that have been activated by initial feature analysis of incoming sounds in the attended ear. The time course of the attention effect in the ERP waveform can be manipulated by changing stimulus speed or complexity ("sensory load"; Hillyard & Picton, 1987). Large, early attention effects (near 100 ms) are evident when a heavy sensory load is imposed on subjects, either by increasing the rate of stimulation or by decreasing stimulus intensity. Large, later attention effects (near 200 to 300 ms) are evident when sensory load is reduced, either by using slower stimulus presentation rates or by increasing stimulus intensity.

The ERP selective attention paradigm has also been used in the investigation of attentional deficits in schizophrenia (Baribeau-Braun, Picton, & Gosselin, 1983; Michie, Fox, Ward, Catts, & McConaghy, 1990). In these studies, the normal attentional difference was not seen in schizophrenic subjects, confirming their reported difficulty in maintaining selective attention. The purpose of this study was to test whether the selective attention paradigm combined with ERP recording might be similarly useful for evaluating decline in attentional and cognitive function during the early stages of HIV infection.

Evaluating the attention system. Posner and Petersen (1990) proposed that the attention system consists of specific neuroanatomical networks, separate from other brain processing networks, which support attentional activation of brain regions involved in rapid target recognition. Both animal and human neurophysiological studies support this concept (Posner & Petersen, 1990). For example, when attentional activation is needed to rapidly detect new auditory information, the attentional system can facilitate activation of an appropriate neuroanatomical network in the auditory system. During divided attention, the human attention system may affect perception of more than one auditory stimulus stream. It can also be used to quickly shift the focus of attention, in order to give a preferred source of incoming

information a higher perceptual priority. Similar processes of attentional activation are thought to occur in the visual system. Neurophysiological studies have identified specific neuroanatomical regions, for both the auditory and visual modalities, that are more highly activated by stimuli in an attended stimulus location or sharing some attributes with attended target stimuli.

If two signals occur close together in time (within approximately 300 ms), as in the case of the dual oddball paradigm used in the present study then the decision to respond to the second signal may interfere with response production for the first signal, resulting in slower responses and possibly poor performance (Pashler, 1992). This interference suggests a maximum rate at which the attentional system can process information and select actions (Pashler, 1992). The neural basis for sequential selection of actions is unknown, but research on the attention system in patients who have had the corpus callosum severed surgically suggest it may be controlled by subcortical pathways (Pashler, 1992). If these pathways are altered or damaged, then the attentional system may no longer be capable of facilitating perception of rapid sequences of sensory inputs.

Näätänen and Picton (1987) suggest that subcortical thalamic structures are involved in the attentional enhancement of the N100 component. If spreading infection damages the thalamic structures or nearby structures, then the attentional system could also be compromised. There is evidence that HIV infection may damage some subcortical regions during the early stages of the disease. For example, lesions in the region of the splenium of the corpus callosum and fornix have been discovered in asymptomatic HIV+ subjects using newly-improved magnetic resonance imaging (MRI), which were not detected using older MRI systems (Kieburtz et al., 1990). It is thus possible that early HIV infection may affect subcortical pathways involved in the attention system, compromising its ability to enhance perception. ERP changes in the selective

attention paradigm may index changes in the attentional system in at least two ways, either by reduction of enhancement in the 100 to 200 ms period, representing loss of attentional sensory sensitization, or by a reduction near 300 ms, possibly representing loss of cognitive resources required to select appropriate responses. An ERP index of attentional system function could be used as an objective method of measuring loss of an HIV subject's ability to activate and successfully engage selective attention processes.

METHODS

Subjects. Six symptomatic and two asymptomatic HIV+ male subjects were tested. These subjects were obtained through the HIV Neurobehavioral Research Center (HNRC) in San Diego. Table 2 shows both the Centers for Disease Control and the Walter Reed staging classifications for each individual. All patients were taking the medication azidothymidine (AZT). Seven normal healthy (HIV-) male (n = 4) and female (n = 3) subjects were also tested at the same time, including collaborative researchers and their subjects from the University of California at San Diego, the Naval Health Research Center, and Scripps Clinic and Research Foundation in San Diego. Unfortunately, the two subject groups were not well matched for gender or educational history because our limited access to the biomagnetometer system severely limited the number of subjects that could be tested. In addition, only one of the seven control subjects was verified as being free of HIV infection by serology testing. However, all of the control subjects were in good health at the time of the study, and none were members of high-risk groups. In our judgement the significant attention-related evoked response differences between the two groups are so provocative that they warrant reporting, albeit with qualification of the generality of these results.

Table 2
Subject Age, Education, Sex, and Illness Demographics

HIV+ SYMPTOMATIC SUBJECTS

SUBJECT	AGE	EDUCATION (YEARS)	SEX	WR	CDC
1	41	15	M	3-5K	4-D
2*	29	19	M	3-5B	4-A
3	34	16	M	5K	4-D
4	29	15	M	5	4-C2
5	35	13	M	5	4-C2
6	32	15	M	5	3

HIV+ ASYMPTOMATIC SUBJECTS

7	45	14	M	2	3
8	32	14	M	3	3
M =	34.6,	15.1			
SE =	±2.0,	±6.4			

Subject Age, Education, and Sex Demographics

HIV- SUBJECTS

SUBJECT	AGE	EDUCATION (YEARS)	SEX
9	30	17+	F
10	36	22	M
11	32	22	M
12	27	19+	M
13	23	18	F
14	30	20	F
15	30	16	M
M =	29.7,	19.1	
SE =	±1.5,	±0.9	

CDC = Centers for Disease Control Classification for HIV Infection
WR = Walter Reed Staging Classification for HIV Infection
Note: CDC 4A,C2,D = opportunistic infections or malignancies diagnostic of AIDS; "A" fever > 1 month, 10% weight loss, diarrhea < 1 month, "C2" oral hairy leukoplakia, multidermatomal herpes zoster, "D" secondary cancers (Kaposi's sarcoma). WR 3-5B,K = WR staging classification ranging from WR3-WR5 [no cutaneous anergy test to confirm exact stage], T-cells count <400 mm³; "B" indicates fevers, weight loss, or diarrhea, "K" indicates Kaposi's sarcoma.
*** Subject No. 2 is excluded from further analyses due to eye artifacts in data.**
t-test Age: ns
t-test Educ.: p<.002

Stimuli. A "dual oddball" selective attention task paradigm was used (Woldorff & Hillyard, 1991). Stimuli consisted of a sequence of 1000 Hz tone pips presented to the left ear, interspersed with a sequence of 3150 Hz tone pips presented to the right ear. The tones were of short duration (14 ms) and presented at a relatively rapid rate (random interstimulus interval [ISI] 126 ms to 326 ms, rectangular distribution), alternating between the two ears (see Figure 1). Ten percent of the tones at each ear were

"targets" and were "soft" in intensity (40 to 43 dB SL) compared to the other 90 percent ("standards") which were relatively louder (55 dB SL). The subject's task was to attend to only the designated ear, and to count targets presented in that ear while ignoring the sounds in the other ear. Subjects were asked to mentally count and at the same time raise their left index finger when they detected target tones in the attended ear. Finger flexions were noted by an experimenter via closed circuit television. The mental target tally was requested from the subject at the end of each experimental run. The designated "attended" ear was alternated across 20 runs (i.e., 10 runs per attended ear). Each run consisted of 250 high-intensity and 25 low-intensity tone pips delivered in each ear in a semirandom order (see Figure 1) in which two targets were never delivered in sequence. Stimuli were air-conducted through plastic tubing into nonmagnetic ear pieces. Stimulus arrival in the ear was recorded, and an approximate 16 ms delay in delivery occurred between the stimulus generation and delivery in the ear. This delay was used in the analysis process as a numerical correction to the ERP epoch lengths.

ERP recording. ERP data were collected from an electrode located at the vertex (central zone [Cz] of the 10/20 International electrode placement system; Jasper, 1958), with left mastoid reference, at a digital sampling rate of 860 Hz using a frequency bandwidth of 0.1 Hz to 200 Hz. The analog data were digitized online using a Hewlett-Packard computer and stored on optical disks for later off-line analysis. Subjects reclined on their right side during recording. The subject's head was positioned on a pillow filled with nylon beads. The pillow was manipulated to conform to the head contours and then fixed into position by creating a vacuum inside the pillow.

Data analyses. Single-trial epochs were recorded to attended and unattended standard and target stimuli. The single trials were then averaged together to yield an average ERP for each of the four

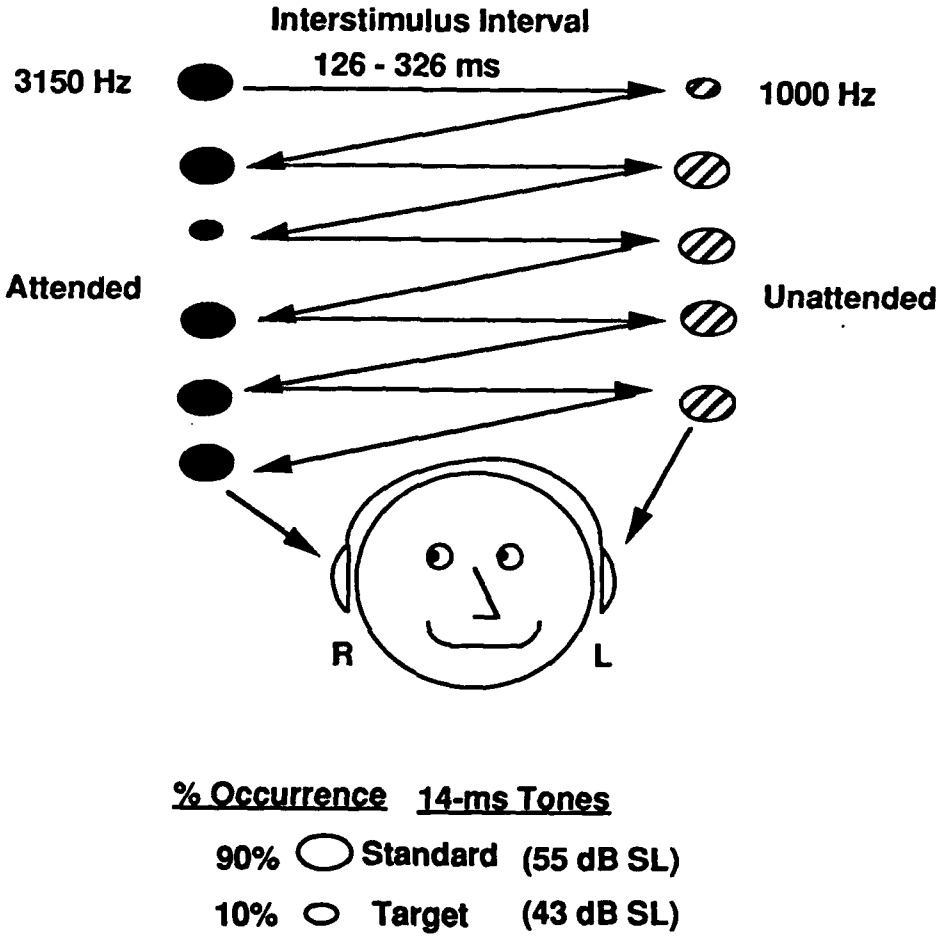

Figure 1. Schematic diagram of the dichotic selective attention task. Stimuli consisted of a sequence of 1000 Hz, 14-ms tone pips presented to the left ear, interspersed at a relatively rapid rate (126 to 136 ms) with a sequence of 3150 Hz, 14-ms tone pips presented to the right ear. Ten percent of the tones at each ear were "targets" (small ovals) and were "soft" in intensity (43 dB SL) compared to the other 90 percent "standards" (large ovals) which were relatively louder (55 dB SL). Subject instructed to attend to only the designated ear (black ovals), and to mentally count targets presented in that ear while ignoring the sounds in the other ear (hatched ovals).

stimulus types. Averaged ERPs to the standard stimuli consisted of 2500 single trials (250 x 10 runs per attended ear); responses to the target stimuli, of 250 single trials (25 x 10 runs per attended ear). An average ERP epoch consisted of a 200-ms prestimulus baseline followed by a 800-ms poststimulus period. Each epoch was then zeroed relative to baseline by subtracting the mean amplitude of the prestimulus baseline period from the poststimulus period. The data from one of the HIV+ subjects (No. 2) were highly contaminated by excessive eye movement, and were excluded from all further analyses.

Responses to standard and target stimuli were analyzed separately. By convention, the "attention effect" consisted of the mean difference between responses to standard stimuli in the attended (Attend condition) and unattended (Inattend condition) channels. The "target effect" consisted of identifying a P300 component in response to attended target stimuli. Also, ERP responses to left and right ear stimuli were analyzed separately because of physical differences between stimuli presented to the left and right ears.

Note that in this experiment three to four stimuli were delivered per second, resulting in three to four single-trial ERPs overlapping one another within the epoch length of the averaged ERP. Woldorff and Hillyard (1991) describe an adjustment procedure to reduce the amount of baseline variability in such averages. Unfortunately, we could not reproduce their procedure on these data, because for technical reasons we were unable to retain the single trial records. In any case, the most significant findings were quite robust despite the inability to correct the distortion from mutually overlapping ERPs.

F-score analysis. This experiment used a repeated measures, mixed factorial design [HIV (2) X Attention (2) X Stimulus Type (2)], with the latter two factors being repeated measures. To

select the portions of the ERP waveforms of greatest statistical significance, each of the 859 frames of the averaged ERPs were submitted to a mixed factorial, repeated measures Analysis of Variance (ANOVA) using an HIV (2) x Attention (2) design. This series of multiple ANOVAs is referred to below as "F-score analysis." To identify regions of significant difference in the ERP waveforms, the 859 F(1,12) values for the two main effects and for their interaction were plotted under the grand average ERPs. For 859 ANOVAs, one would expect to find 43, 21 and 9 spurious results at alpha levels of .05, .025, and .01, respectively. To minimize the likelihood of committing Type I error, only F-score peaks that exceeded the .025 alpha level were considered significant. To reduce the probability of a Type I error further, ERP regions that corresponded to the significant F-score peaks were then analyzed using a low-pass measure (40-ms mean area amplitude) centered on each significant F-score peak. This was done to confirm that a broad, slow-wave region of the waveforms, rather than an isolated time point, varied significantly with experimental conditions. To obtain the 40-ms mean area amplitude measures, the ERP data were smoothed using a 40-ms moving average time window. The smoothing transformed the data into a series of mean area amplitudes, each point representing the mean area of 40 ms of data. Mean area amplitudes corresponding to the latencies of the significant peaks in the F-score analysis were then subjected to further analysis by ANOVA. Significant interactions found in the low pass data ANOVAs were further examined using one-way ANOVAs with pair-wise comparisons.

Results

Right Standards

Attention effect. Grand average ERP responses to the right standard stimuli, and point-by-point F-scores are displayed in Figure 2. F-score analysis identified main effects of Attention at five latencies in the ERP epoch (88, 223, 339, 480, and 602 ms). ANOVAs on mean area amplitudes confirmed the F-score analysis in each case. Table 3 contains a summary of the effects of Attention on mean area amplitudes. Results indicate that larger positive and negative ERP components were generated when the right standard stimuli were in the attended channel (Attend condition) as compared to when the same stimuli were in the unattended channel (Inattend condition).

Table 3. Right Standards - Summary of Main Effects of Attention by Mean Area Amplitude ANOVAs

Latency (ms)	F(1,12)	p
88	53.24	.000
223	11.95	.005
339	17.38	.001
480	12.73	.004
602	10.18	.008

HIV effect. F-score analysis yielded a modest ($p < .025$) group main effect of HIV at 60 ms; however, the ANOVA on mean area amplitudes failed to reach significance.

HIV by Attention interaction. F-score analysis also identified an HIV x Attention interaction centered at 522 ms, which was confirmed by an ANOVA on mean area amplitudes, $F(1,12) = 6.98$, $p < .025$. The interaction was further analyzed using pair-wise comparisons. Table 4 contains a summary of the group means for the interaction and the pair-wise comparisons. These results suggest that the HIV+ group showed an effect of Attention at this latency, whereas the HIV- group did not.

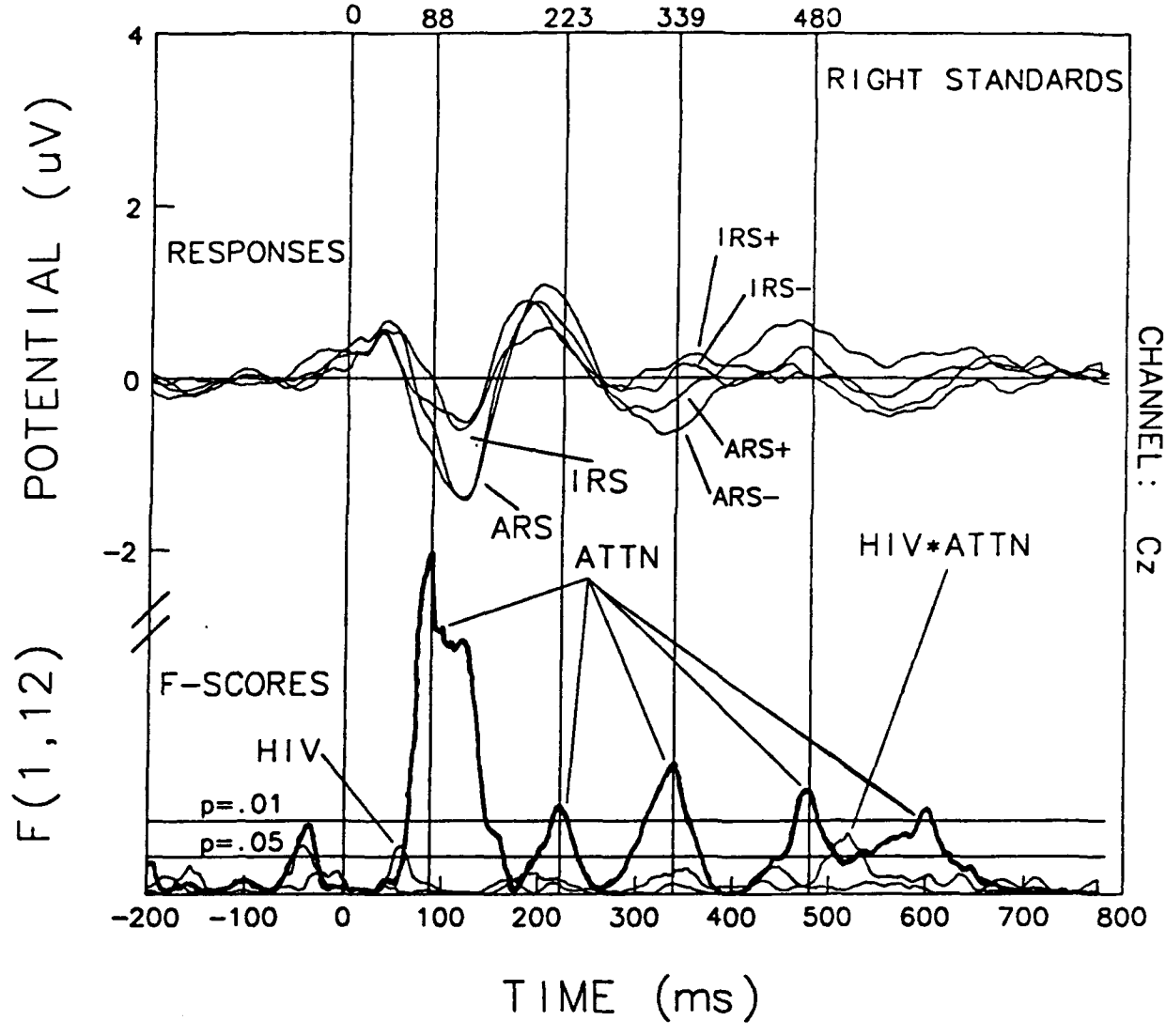

Figure 2. ERPs: Grand average waveforms evoked by attended (ARS) and unattended (IRS) right standard stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN). Bold trace indicates Attention effect in the F scores. Horizontal lines indicate statistical probabilities. Vertical lines indicate latencies.

Table 4. Right Standards - Summary of Group Mean Area Amplitudes and Pair-wise Comparisons for the HIV x Attention Interaction

Group	Attention	522 ms Mean (μV)	SD
HIV+	Attend	0.31	0.24
	Inattend	-0.28	0.35
HIV-	Attend	-0.11	0.33
	Inattend	-0.07	0.28

	d.f.	522 ms F	p
Within Comparisons			
HIV+: Attend vs Inattend	1,6	7.48	.018
HIV-: Attend vs Inattend	1,6	0.06	ns
Between Comparisons			
Attend: HIV+ vs. HIV-	1,12	7.36	.019
Inattend: HIV+ vs. HIV-	1,12	1.54	ns

To demonstrate the magnitude and timecourse of an effect (i.e., HIV, Attention, HIV x Attention), ERP responses to the unattended standards were subtracted from the attended ones for each of the 14 subjects. Grand average difference waves are shown in Figure 3. Note the magnitude of the Attention effect which is responsible for the most significant findings in these analyses.

Right Targets

Attention effect. Grand average ERP responses to the right target stimuli and point-by-point F-scores are displayed in Figure 4. F-score analysis yielded significant main effects of Attention at two latencies (126 ms and 399 ms). At 126 ms, an ANOVA on mean area amplitude confirmed greater N100 amplitudes were generated when the targets were in the attended channel (M = -1.47 μV) than in the unattended channel (M = 0.03 μV), $F(1,12) = 20.09$, $p < .002$. At 399 ms, an ANOVA on the mean area amplitudes also confirmed greater positive (P300) amplitudes were generated when stimuli were attended (M = 1.95 μV versus M = 0.17 μV; $F(1,12) = 10.03$, $p < .009$). These results are illustrated in Figure 4, which also shows a dramatic difference in target responses in the two groups.

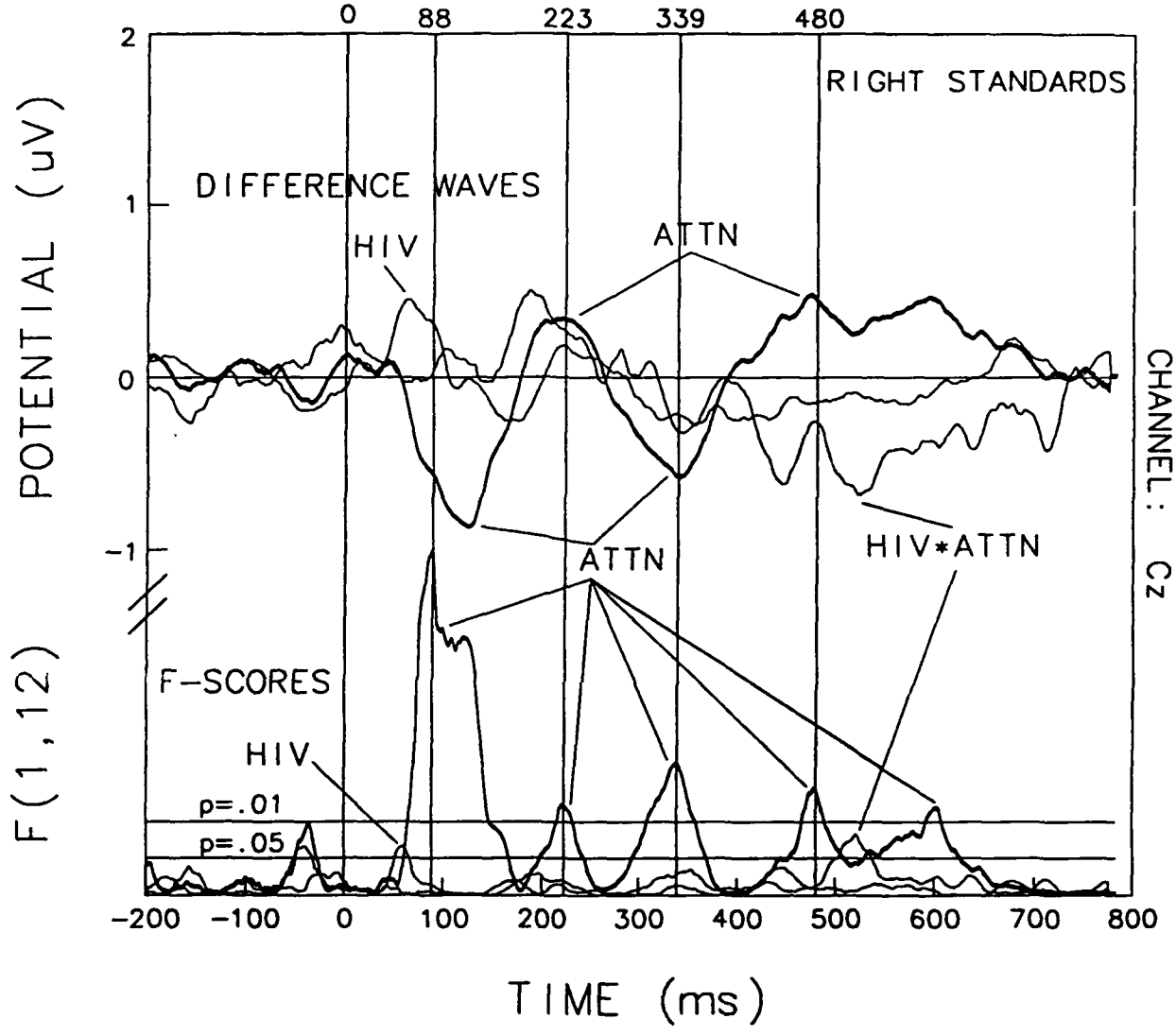

Figure 3. ERPs: Grand average difference waveforms (ARS - IRS) to right standard stimuli at scalp site Cz from both HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN). Bold traces indicate Attention effect in the difference waves and in the F scores.

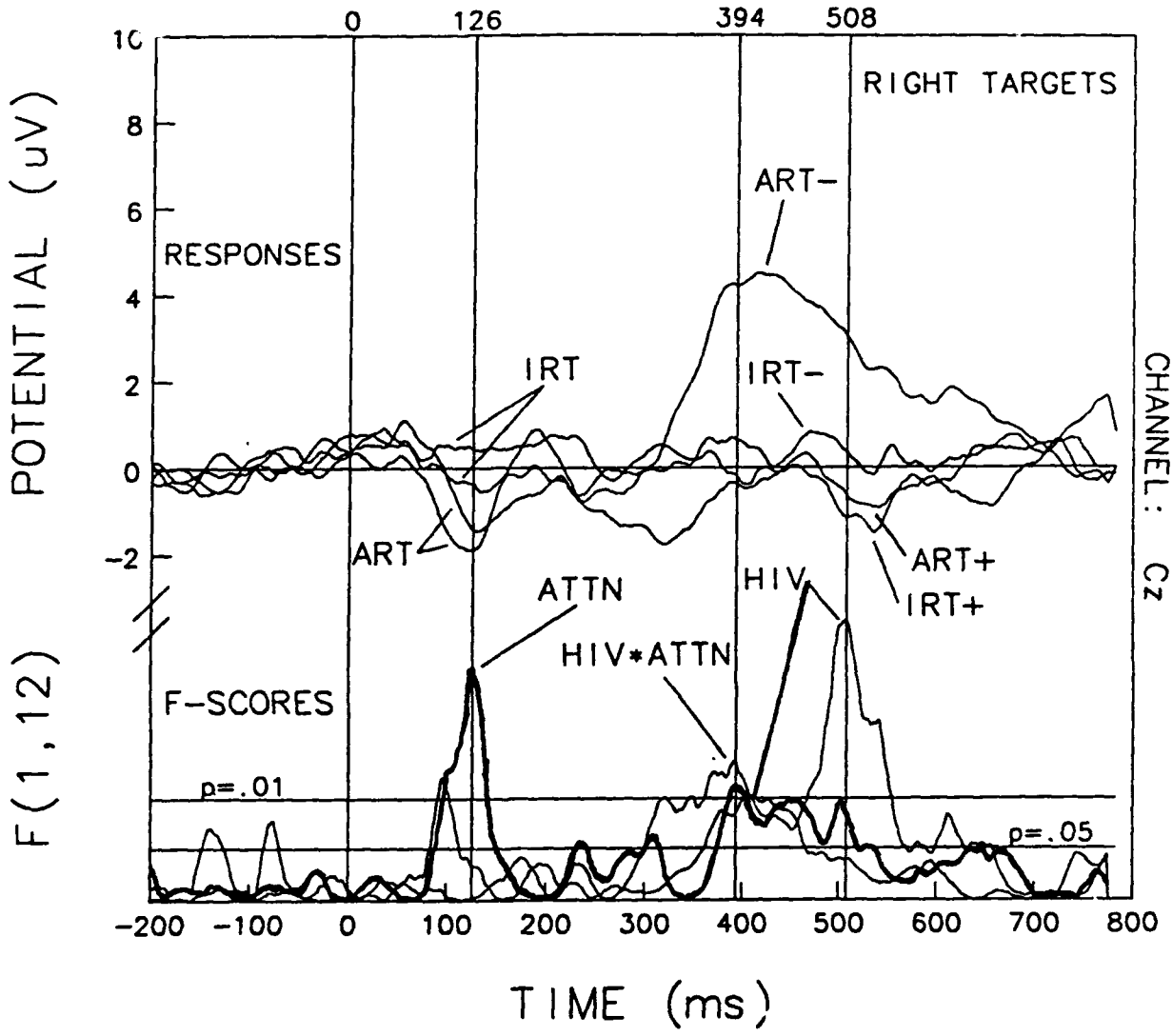

Figure 4. ERPs: Grand average waveforms evoked by attended (ART) and unattended (IRT) right target stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN).

HIV effect. F-score analysis identified significant main effects of HIV at two latencies (408 ms and 508 ms). ANOVAs on mean area amplitudes confirmed significantly more positive amplitudes were generated in this region by the HIV- group. At 408 ms, mean area amplitude values were positive ($\underline{M}$ = 2.42 μV) for the HIV- group, and negative ($\underline{M}$= −0.28 μV) for the HIV+ group, and this difference was significant, $\underline{F}(1,12) = 8.54$, $\underline{p} < .014$. At 508 ms, ANOVAs on mean area amplitudes confirmed that the HIV- group generated significantly larger amplitudes ($\underline{M}$ = 1.66 μV) compared to the HIV+ group ($\underline{M}$ = −0.81 μV), and this difference was also significant, $\underline{F}(1,12) = 23.75$, $\underline{p} < .001$.

HIV by Attention interation. F-score analysis also identified significant HIV x Attention interactions at two latencies (97 ms and 394 ms). These were further analyzed using pair-wise comparisons. Table 5 contains a summary of the group means for the interactions and pair-wise comparisons. These results suggest that at approximately 97 ms the HIV+ group showed an Attention effect, whereas the HIV- group did not. This is illustrated in Figure 4. At 394 ms the HIV- group generated a large, positive (P300) component when the targets were in the attended channel only. In contrast, the HIV+ group did not produce any significant components in this region in either attention condition. Each subject's averages are displayed in Figures 5 and 6 to further illustrate the difference that appears in the grand averages in Figure 4. Note in Figure 5a that most of the seven HIV- subjects produced sizeable P300 components during the Attend condition compared to Figure 6a in which two HIV+ subjects may have produced small P300-type components during the Attend condition. Grand average difference waveforms are shown in Figure 7. Note the magnitude of the HIV effect and the HIV x Attention interaction in the region of the P300 (394 ms) which is the region of the most significant findings in these analyses.

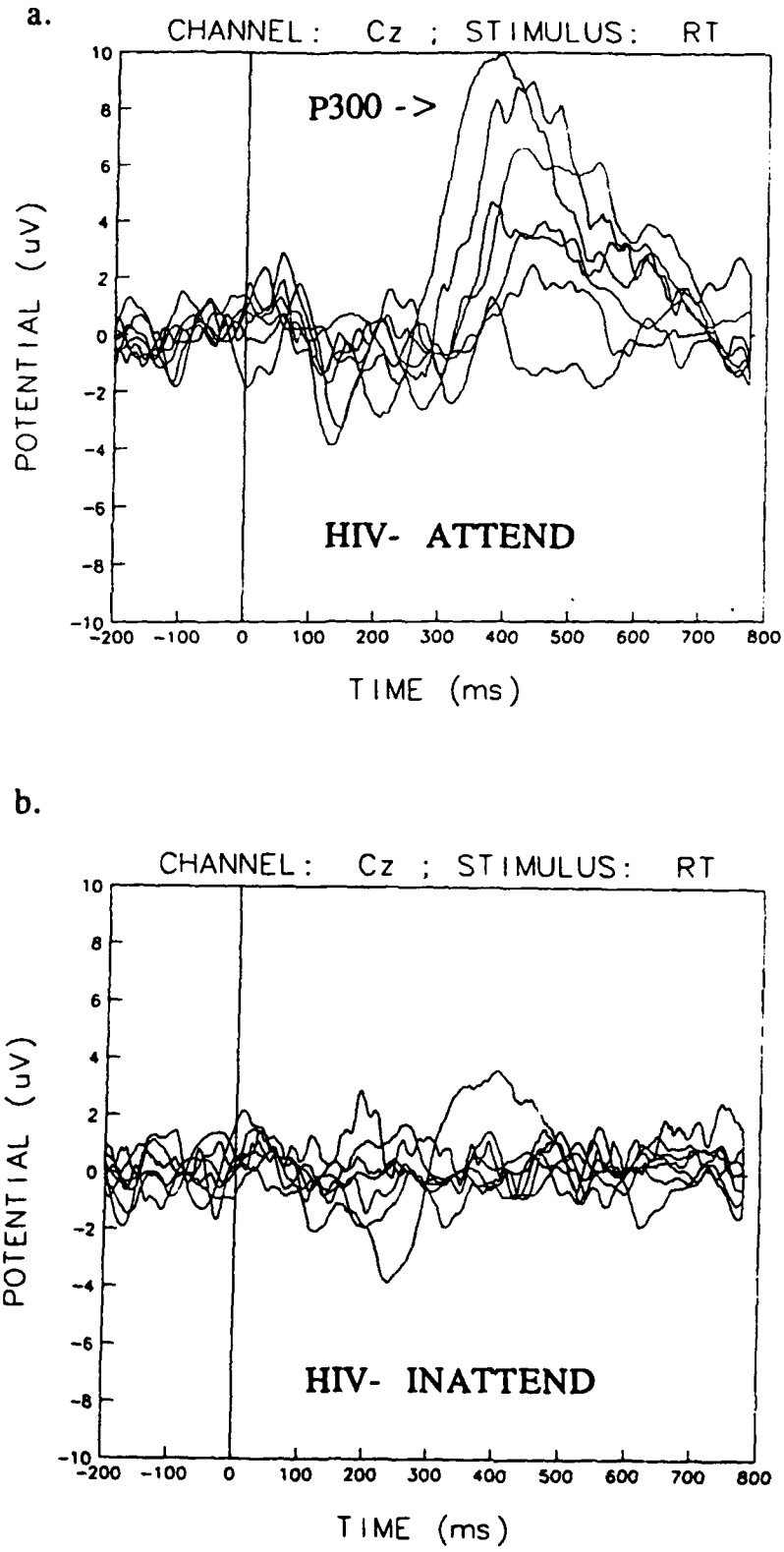

Figure 5. a. Seven average waveforms evoked by attended right target stimuli at scalp site Cz from seven HIV- subjects. The P300 component is evident in most of these ERPs. b. Seven average waveforms evoked by unattended right target stimuli from the same subjects.

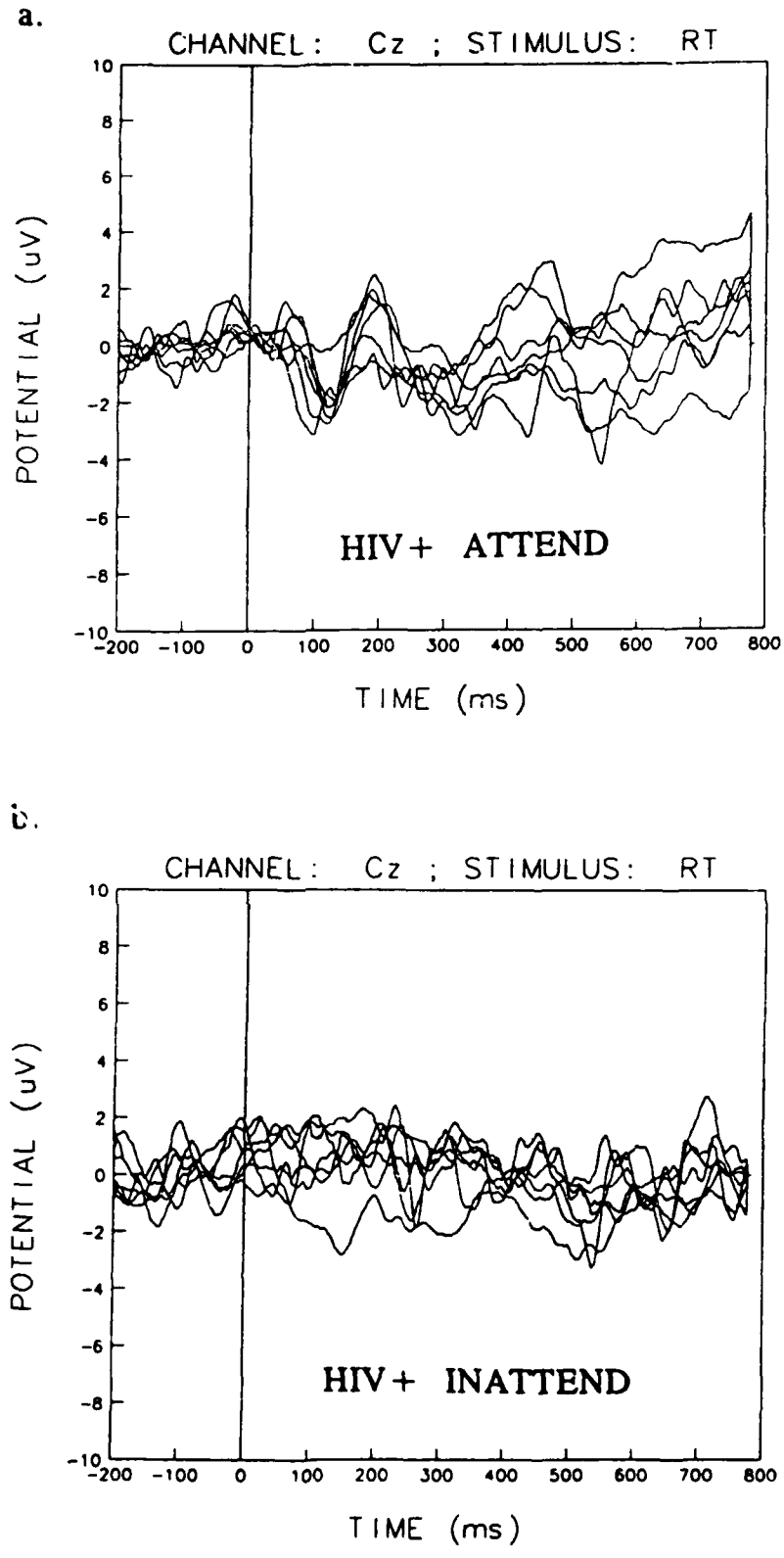

Figure 6. a. Seven average waveforms evoked by attended right target stimuli at scalp site Cz from seven HIV+ subjects. The P300 component is not evident in most of these ERPs. b. Seven average waveforms evoked by unattended right target stimuli from the same subjects.

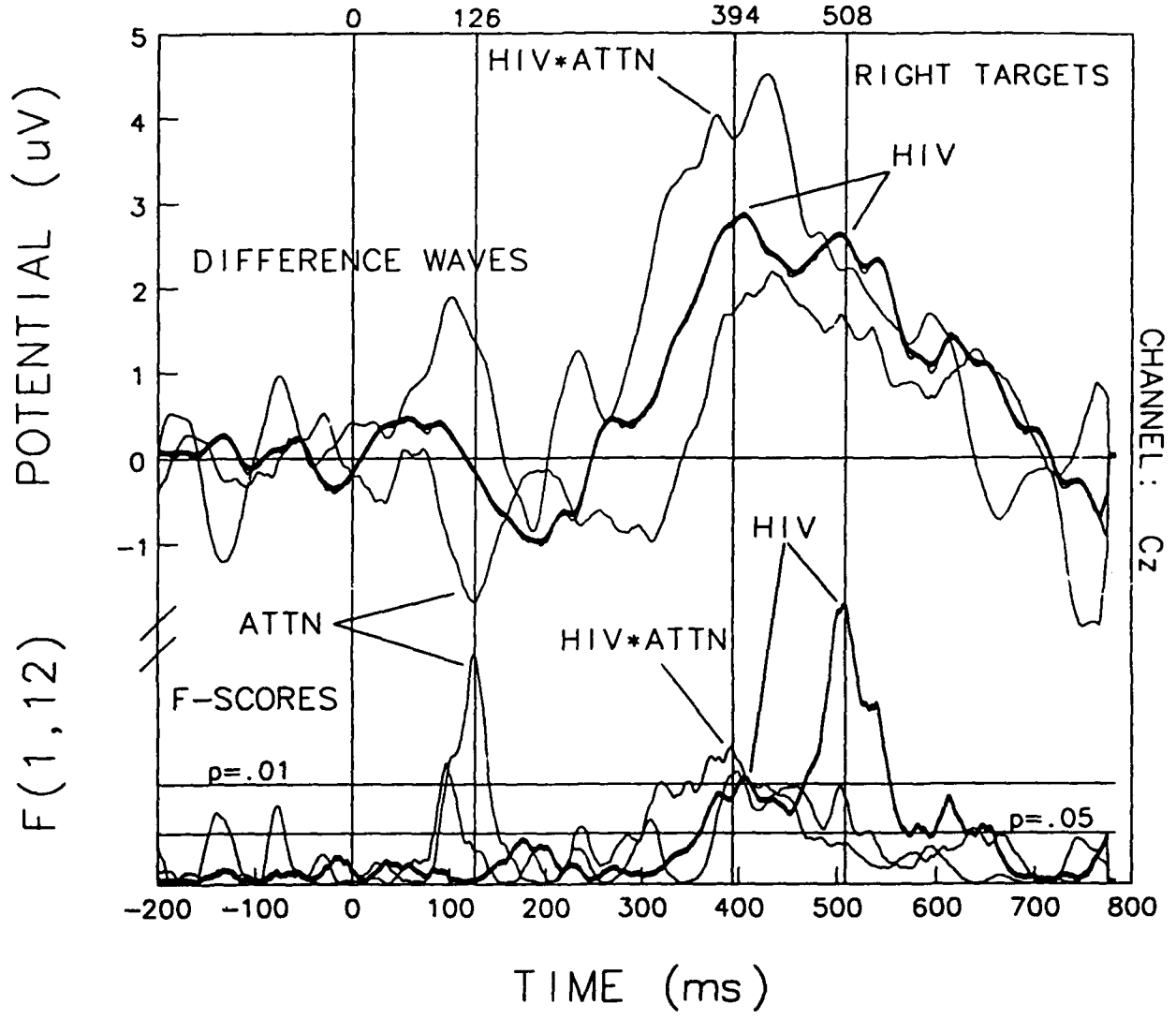

Figure 7. ERPs: Grand average difference waveforms (ART - IRT) to right target stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN).

Table 5. Right Standards - Summary of Group Mean Area Amplitudes and Pair-wise Comparisons for the HIV x Attention Interactions

Group	Attention	97 ms Mean (μV)	97 ms SD	394 ms Mean (μV)	394 ms SD
HIV+	Attend	-1.19	0.97	-0.45	1.28
	Inattend	0.44	1.19	-0.22	0.40
HIV-	Attend	-0.10	0.60	4.26	3.52
HIV-	Inattend	-0.10	0.54	0.58	1.37

Pair-wise Comparisons	d.f.	97 ms F	97 ms p	394 ms F	394 ms p
Within Comparisons					
HIV+: Attend vs. Inattend	1,6	17.11	.006	0.25	ns
HIV-: Attend vs. Inattend	1,6	0.00	ns	13.71	.010
Between Comparisons					
Attend: HIV+ vs. HIV-	1,12	6.41	ns	11.05	.006
Inattend: HIV+ vs. HIV-	1,12	1.21	ns	2.16	ns

Left Standards

Results for left ear stimuli were quite similar to those for right ear stimuli.

Attention effect. Results for left standard stimuli, shown in Figure 8, were similar to results for right standards. F-score analysis identified significant main effects of Attention at four peak time points (124, 216, 351, and 580 ms). The ANOVAs on mean area amplitudes confirmed the F-score analysis. Table 6 contains a summary of the Attention effects. These results indicate that greater positive and negative components were generated in these time periods when the left standard stimuli were in the attended channel.

Table 6. Left Standards - Summary of Mean Area Amplitudes and Main Effects of Attention

Latency (ms)	Attend Mean (μV)	Attend SD	Inattend Mean (μV)	Inattend SD	F(1,12)	p
124	-1.39	0.40	-0.70	0.27	39.46	.000
216	1.03	0.41	0.73	0.44	10.9[illegible]	.006
351	-0.48	0.34	0.07	0.38	27.[illegible]	.000
580	0.31	0.43	-0.24	0.29	2[illegible]	.000

HIV effect. F-score analysis identified significant effects of HIV at three latencies (235, 465, and 601 ms). These were

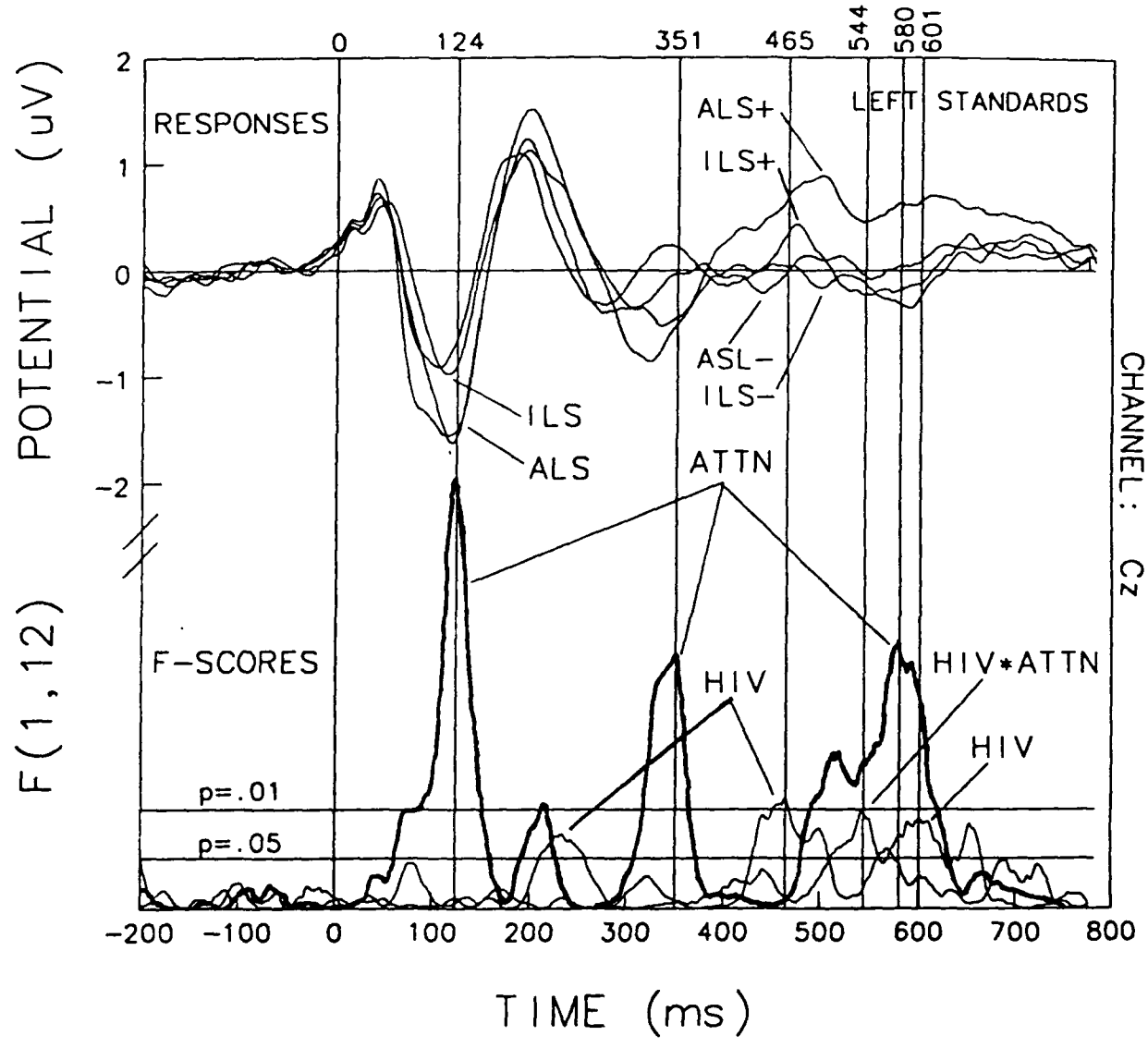

Figure 8. ERPs: Grand average waveforms evoked by attended (ALS) and unattended (ILS) left standard stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN).

confirmed by ANOVAs on mean area amplitudes in each case. Table 7 contains a summary of the HIV main effects. These results indicate that smaller positive (P200) amplitudes were generated by the HIV+ group at 235 ms; however, greater amplitudes were generated by the HIV- group at 465 ms and 601 ms.

Table 7. Left Standards - Summary of Mean Area Amplitudes and Main Effects of HIV

Latency	HIV+		HIV-			
(ms)	Mean(μV)	SD	Mean(μV)	SD	F(1,12)	p
235	0.22	0.33	0.74	0.46	7.87	.016
465	0.49	0.54	0.01	0.28	10.06	.008
601	0.29	0.50	-0.06	0.33	9.48	.010

HIV by Attention interaction. F-score analysis also identified a significant HIV x Attention interaction centered at 544 ms. Table 8 contains a summary of the group means for the interactions and the pair-wise comparisons. These results indicate that the HIV+ group, but not the HIV- group, generated larger positive potentials at and near 544 ms when the stimuli were in the attended channel.

Table 8. Left Standards - Summary of Group Mean Area Amplitudes and Pair-wise Comparisons for the HIV x Attention Interactions

		544 ms	
GROUP	Attention	Mean(μV)	SD
HIV+	Attend	0.49	0.43
	Inattend	-0.20	0.33
HIV-	Attend	-0.01	0.32
	Inattend	-0.14	0.27

		544 ms	
Pair-wise Comparisons	d.f.	F	p
Within Comparisons			
HIV+: Attend vs. Inattend	1,6	12.53	.012
HIV-: Attend vs. Inattend	1,6	2.61	ns
Between Comparisons			
Attend: HIV+ vs. HIV-	1,12	6.28	.028
Inattend: HIV+ vs. HIV-	1,12	0.17	ns

To demonstrate the differences between the groups in these two conditions, grand average difference waveforms are shown in Figure 9.

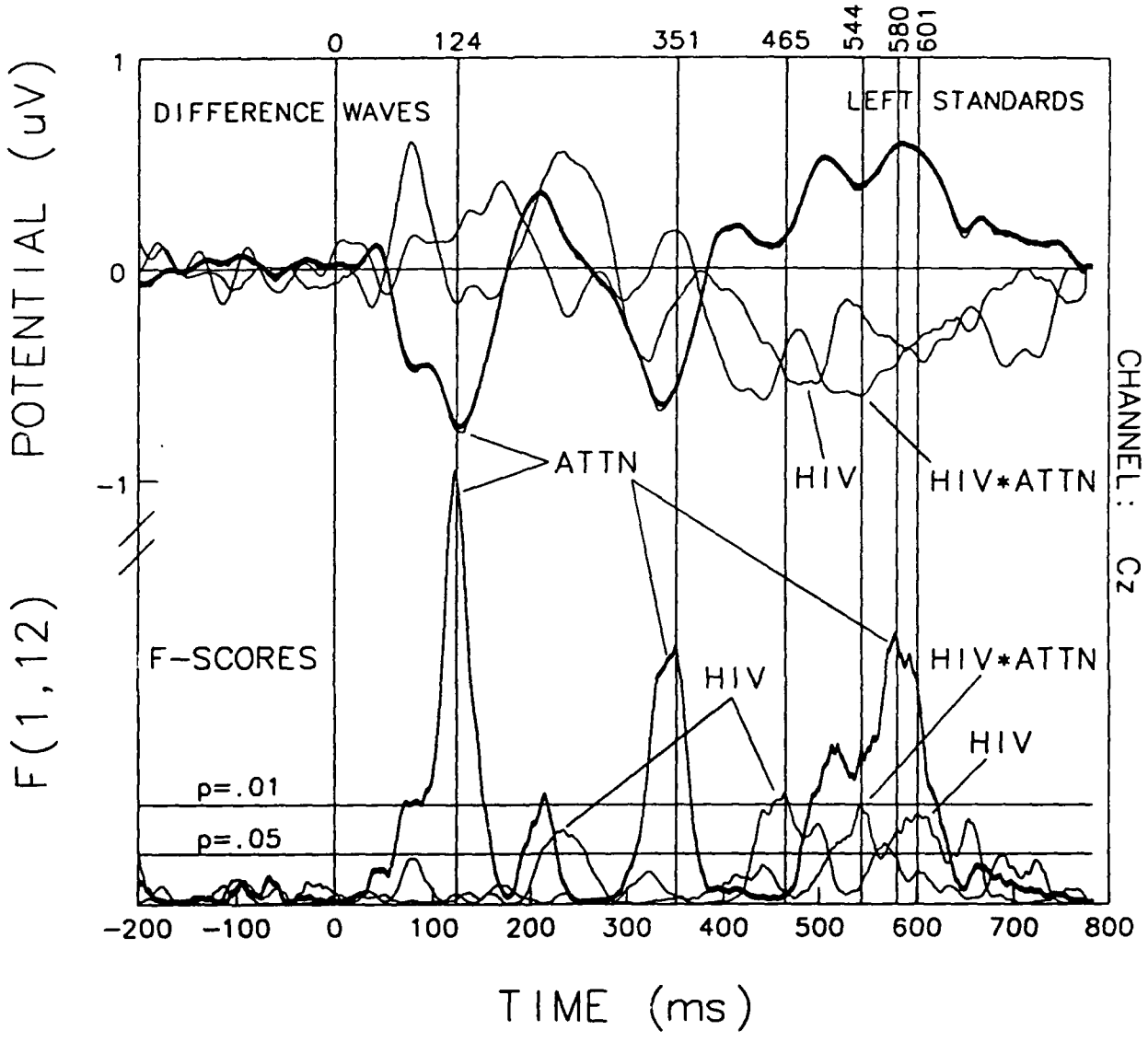

Figure 9. ERPs: Grand average difference waveforms (ALS - ILS) to left standard stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN).

Left Targets

Attention effect. Responses to left targets, shown in Figure 10, resembled those to right targets. F-score analysis identified significant effects of Attention in three time periods (153, 251, and 380 ms). ANOVAs on mean area amplitudes confirmed the F-score analysis. Table 9 summarizes these effects. Results indicate that overall, larger negative responses were generated at the earlier two latencies when the targets were in the attended channel, and larger positive responses (P300) at 380 ms.

Table 9. Left Targets - Summary of Mean Area Amplitudes and Main Effects of Attention

Latency	Attend		Inattend			
(ms)	Mean(μV)	SD	Mean(μV)	SD	F(1,12)	p
153	-1.12	0.92	-0.11	0.80	13.02	.004
251	-1.81	1.06	-0.18	1.10	62.31	.000
380	2.43	3.85	0.17	1.61	7.31	.019

HIV effect. F-score analysis identified significant effects of HIV at two latencies (175 and 386 ms). At 175 ms, a mean area amplitude ANOVA confirmed significantly more positivity for the HIV+ group (M = 0.31 μV) than the HIV- group (M = -0.79 μV), $F(1,12) = 7.24$, $p < .019$. At 386 ms, a mean area amplitude ANOVA indicated significantly greater amplitudes for the HIV- group (M = 2.88 μV) as compared to the HIV+ group (M = -0.21 μV), $F(1,12) = 12.32$, $p < .005$.

HIV by Attention interaction. The F-score analysis identified significant HIV x Attention interactions at three latencies (286 ms, 353 ms, and 392 ms). The interactions were further analyzed using pair-wise comparisons. Table 10 lists the means for the interactions and pair-wise comparisons. These results suggest that at 286 ms, the HIV+ group had a negative-going attention effect,

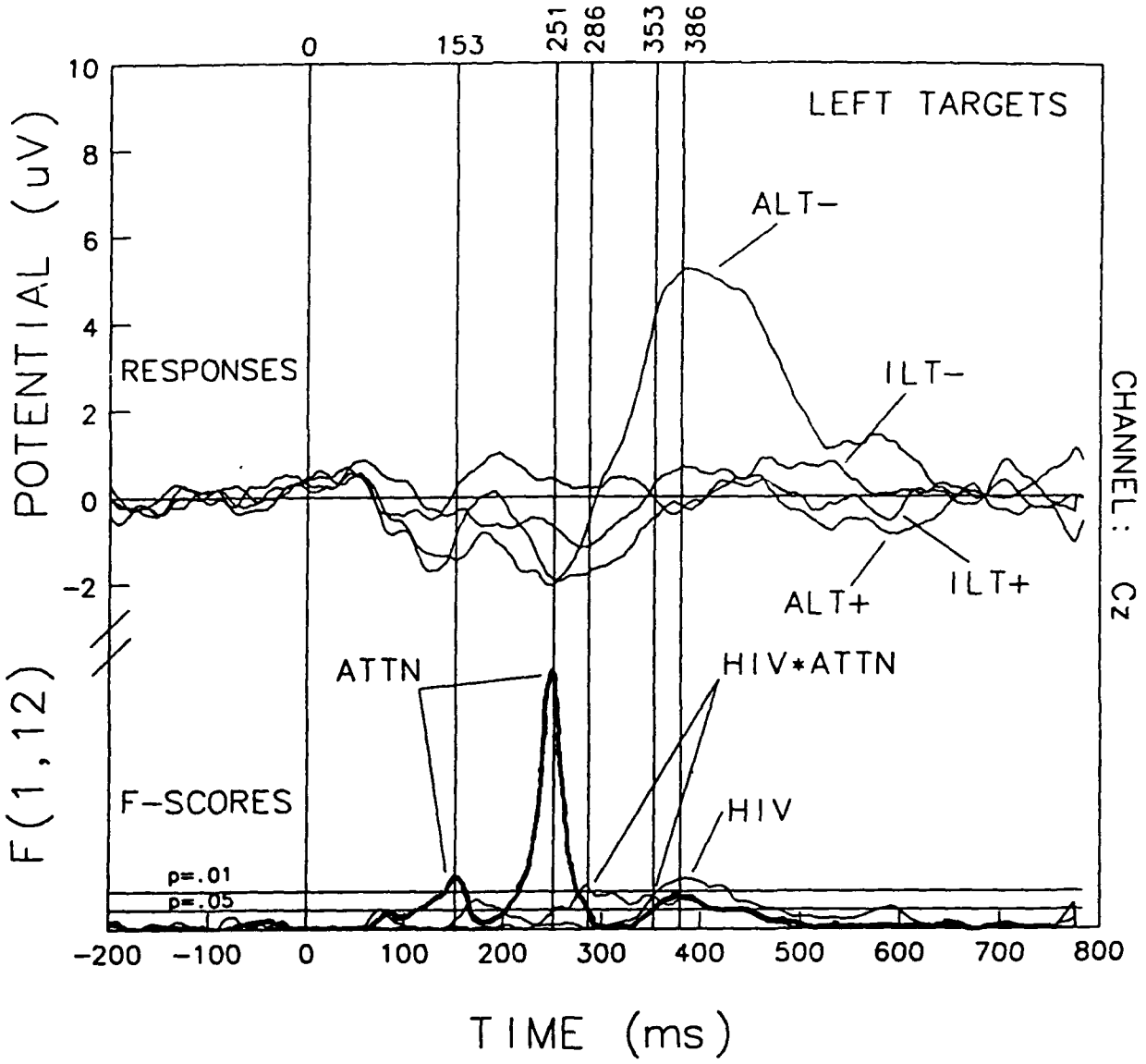

Figure 10. ERPs: Grand average waveforms evoked by attended (ALT) and unattended (ILT) left target stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN).

whereas the HIV- group had a positive-going effect. At 392 ms, the HIV- group generated, as expected, a large P300 component when the targets were in the attended channel, but the HIV+ group did not.

Table 10. Left Targets - Summary of Group Mean Area Amplitudes and Pair-wise Comparisons for the HIV x Attention Interactions

		286 ms		353 ms		392 ms	
Group	Attention	Mean (μV)	SD	Mean (μV)	SD	Mean (μV)	SD
HIV+	Attend	-1.74	1.01	-0.50	1.11	-0.18	1.59
	Inattend	0.21	0.70	-0.03	0.91	-0.18	1.27
HIV-	Attend	-0.59	1.15	3.90	3.59	5.15	3.66
	Inattend	-1.08	1.10	0.21	1.77	0.60	1.86

		286 ms			353 ms		392 ms	
Pair-wise Comparisons		d.f.	F	p	F	p	F	p
Within Comparisons								
HIV+:	Attend vs. Inattend	1,6	34.66	.001	0.77	ns	0.00	ns
HIV-:	Attend vs. Inattend	1,6	0.50	ns	6.60	ns	8.07	ns
Between Comparisons								
Attend:	HIV+ vs. HIV-	1,12	3.96	ns	9.59	.009	12.45	.004
Inattend:	HIV+ vs. HIV-	1,12	6.83	0.02	0.10	ns	0.85	ns

To further demonstrate the effects of group and attention on the ERP waveforms, grand average difference waveforms are displayed in Figure 11.

Detected targets

The number of reported target detections recorded for each subject were analyzed by ANOVA using an HIV (2) x Ear Attended (2) two-way mixed factor design. The ANOVA yielded a significant group main effect of HIV, $F(1,12) = 6.93$, $p < .025$, and a main effect of Ear Attended, $F(1,12) = 8.33$, $p < .025$. The HIV- group reported a larger number of detected targets (M = 17.7 per 25 targets or 71%, SE $\pm$ 0.46) than did the HIV+ group (M = 11.9 per 25 targets or 48%, SE $\pm$ 0.36). Left ear targets were more often detected (M = 15.93 per 25 targets or 64%, SE $\pm$ 0.50) than the right ear targets (M = 13.74 per 25 targets or 55%, SE $\pm$ 0.45).

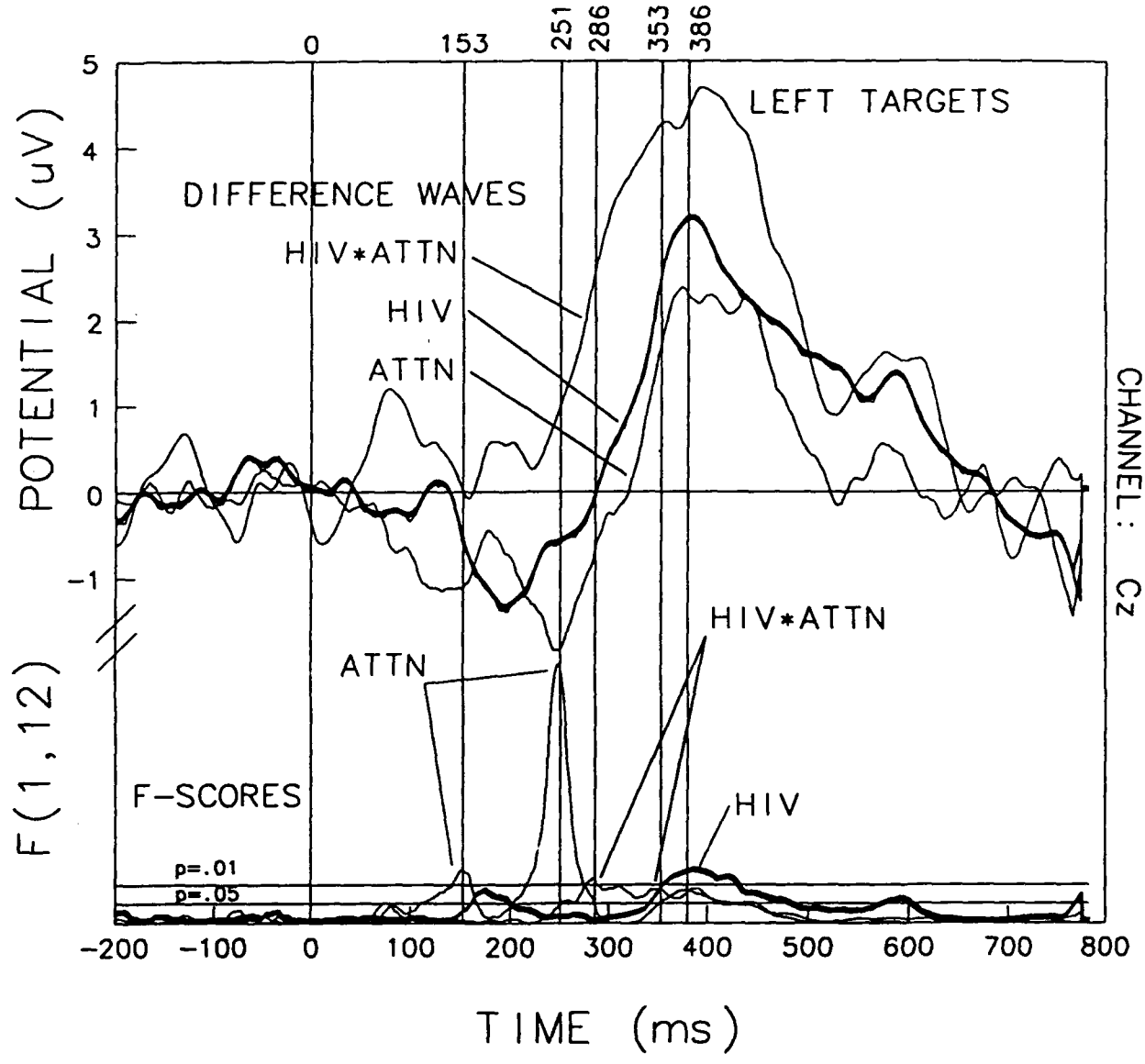

Figure 11. ERPs: Grand average difference waveforms (ALT - ILT) to left target stimuli at scalp site Cz from HIV+ and HIV- groups. F-scores: Plot of F(1,12) scores from 859 two-way, mixed-factor, repeated measures ANOVAs for two main effects (HIV, ATTN) and their interaction (HIV x ATTN).

DISCUSSION

These ERP results suggest differences in cognitive processing between the HIV- and HIV+ subjects. Our results are similar to other ERP cognitive studies which have focused primarily on advanced-staged HIV+ individuals suffering from opportunistic infections. However, our study used a more cognitively demanding task, the dual oddball paradigm, than other studies, which used the less-demanding single oddball paradigm. This difference in experimental design may have resulted in more dramatic evoked response differences between groups than in other ERP studies. Our results suggest that all of the HIV-infected subjects (including the two asymptomatic subjects) had difficulty processing rapidly-presented auditory stimuli. This conclusion is reinforced by their behavioral performance, which was lower than that of the HIV- group, although group differences in educational background may have been a factor in the performance difference.

Hillyard and Picton (1987) have suggested that the time course of the difference wave, termed the negative difference or "Nd" wave, representing the Attention effect in the selective paradigm, is due to an additional negative slow wave ERP component that overlaps the N100 and extends beyond it, rather than modulating the amplitude of the N100 itself. Figures 3 and 9 indicate that early in the Nd wave, in the region of the N100 and P200, both groups had augmented responses to the attended standard stimuli, suggesting that within the first 200 ms after stimulus onset, attention activation may have been intact in these HIV+ subjects.

There were, however, later group differences in attentional activation to the standard stimuli, near 500 ms, that may index compromise to the attentional system. These differences appeared to consist of a late positive attentional activation in the HIV+ group (see Figures 2 and 8) for both right and left standard stimuli delivered to the attended channel. Magnetic resonance

scans performed on the HIV+ subjects indicated that at least 5 HIV+ subjects had cortical volume loss[1]. We speculate from previous research (Kieburtz et al., 1990) that this neuronal loss might also have affected some part of the brain attentional system, making it difficult for the HIV+ subjects to process the rapidly presented stimuli and quickly distinguish between target and standard stimuli in the attended channel. The late attention difference wave for the standard stimuli might represent the late application of additional attentional resources in the HIV+ subjects to make the target/standard distinction, whereas in the HIV- group, this comparison was completed earlier.

The presence of a P300 evoked by attended target stimuli is now well accepted as an indicator of cognitive activation involving stimulus discrimination, categorization, and response selection for task-relevant stimuli (Duncan-Johnson & Donchin, 1982). In this experiment, only the HIV- group produced distinct P300 waveforms to attended targets (see Figures 4,5a and 10). The P300 results suggest cognitive processing differences between the two groups. These differences may correspond with Pashler's (1992) "bottleneck" theory of response selection. According to this theory, there exists a maximum rate to which information is processed and responded. HIV may have compromised the ability to process and respond to rapid sequences of information. Instead of large P300s, indicative of an intact response-selection process, the HIV+ subjects produced no significant P300s, suggesting a nonintact response-selection process. Furthermore, they reported on average fewer (48%) targets than the HIV- group (71%). Together, these results suggested the HIV+ group had diminished cognitive processing abilities.

Other HIV, ERP studies (Goodin et al., 1990; Grotemeyer, et

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[1] Consultation reports on MRI scans were provided by HNRC, San Diego, CA.

al. 1991; Messenheimer et al., 1992) using the single oddball paradigm have reported increased P300 latencies and/or reduced amplitudes in HIV+ patients suggesting that the response-selection process was altered by HIV. Our results concur with theirs, but our more complex and difficult dual oddball paradigm may be a better method of evaluating the response-selection process in HIV patients.

In conclusion, it appears from these ERP and behavioral results that the HIV+ subjects were able to focus their attention on the attended ear, but they may have been unable to process as efficiently the rapid sequences of stimuli presented during the task. The most dramatic effect found is the almost complete disappearence of the P300 to attended targets in the HIV+ group. The effect of HIV infection on the P300 may have been enhanced by the more complex and difficult dual oddball paradigm. A second finding was the prolonged Attention effect produced by the HIV+ subjects to standard stimuli in the attended ear.

The auditory selective attention task is a useful tool in evaluating cognitive processing abilities, and potentially useful in monitoring HIV's destructive effects to the brain. This task is not a measure of the auditory system per se, but rather perception and cognitive processing abilities which are resources that are associated with all sensory modalities. Clearly, replication of these results is needed using more subjects and a better matched control group. Blood tests are also necessary to confirm the HIV-status of the control group. Evaluation of depression/anxiety levels in subjects, which could affect the ERPs (e.g., Thier, Axmann, & Giedke, 1986), should also be carried out. Finally, more exact performance measures including reaction times will be useful. If careful replication confirms these findings, then Navy medical leaders might consider adopting these measures as a routine assessment procedure assisting them in deciding whether selected HIV+ personnel remain cognitively "fit for duty."

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This study assessed the cognitive performance and brain potentials of a pilot group of subjects infected with the human immunodeficiency virus (HIV) in an attention-demanding task, in order to understand whether HIV alters attentional processes. Event-related brain potentials (ERPs) were recorded from both HIV-infected (HIV+) and healthy control subjects while attending a sequence of tones in one ear and ignoring another sequence in the opposite ear. The subject's task was to detect target tones embedded in the attended sequence. ERPs elicited to the target tones by the HIV+ group did not have P300 components in them. (P300 is considered to index mental activity used during target detection.) Furthermore, the HIV+ subjects detected fewer targets (48%) than the control subjects (71%). Also, ERPs elicited to nontarget tones by the HIV+ group showed abnormal changes in the waveform at about 500 milliseconds suggesting a delay in the completion of attentional activation. Although the results need to be replicated with a larger group, they suggest that an objective, non-invasive method of evaluating changes in the attentional capabilities of HIV+ personnel is feasible.

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